ATACs: A Unique New Mode of Action to Fight Cancer

Deutsche Biotechnologietage - 28<sup>th</sup> March 2023
Safe Harbor

Forward looking statements

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Heidelberg Pharma – a Clinical Stage Company

Our Company

~ 110 employees

Headquarters in Heidelberg area, Germany

Listed on Frankfurt Stock Exchange: HPHA

Clinical stage biotech

Complete in-house research capabilities

Cash reach until mid-2025
(as of November 2022)

Our Approach

Inhibition of RNA Polymerase II

Targeted delivery via antibodies (ADC technology)

Use Amanitin as toxic payload (ATAC technology)

Our Mission

Provide new options in cancer therapy

Overcome resistance mechanisms

Kill dormant tumor cells

Develop biomarker for patient stratification
## Growing Pipeline of Proprietary and Partnered Programs

<table>
<thead>
<tr>
<th>Product</th>
<th>Target</th>
<th>Indication</th>
<th>Research</th>
<th>Preclinic</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDP-101</td>
<td>BCMA</td>
<td>Multiple Myeloma (DBCL/CLL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Huadong (Asia)</td>
</tr>
<tr>
<td>HDP-102</td>
<td>CD37</td>
<td>NHL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Huadong (Asia, option)</td>
</tr>
<tr>
<td>HDP-103</td>
<td>PSMA</td>
<td>Prostate cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Huadong (Asia)</td>
</tr>
<tr>
<td>HDP-104</td>
<td>GCC</td>
<td>Gastrointestinal (e.g., CRC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Huadong (Asia, option)</td>
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<tr>
<td>HDP-XX</td>
<td>n/a</td>
<td>Solid &amp; hematological malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proprietary</td>
</tr>
</tbody>
</table>

### ATAC pipeline

### ATAC partners

- **MGTA-ATACs**
  - CD117, CD45
  - HSCs, conditioning programs for blood cancers and genetic diseases
  - Magenta
  - All programs stopped

- **TAK-ATAC**
  - n/a
  - Oncology
  - Takeda

- **CHIOME-ATAC**
  - CDCP1
  - Oncology
  - Chiome

### Legacy assets

<table>
<thead>
<tr>
<th>Product</th>
<th>Target</th>
<th>Indication</th>
<th>Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLX250-CDx</td>
<td>CA-IX</td>
<td>Renal and urothelial carcinoma, TNBC</td>
<td>Telix</td>
</tr>
<tr>
<td>TLX250</td>
<td>CA-IX</td>
<td>Renal carcinoma</td>
<td>Telix</td>
</tr>
<tr>
<td>RHB-107</td>
<td>CA-IX</td>
<td>Oncology/GI, Covid-19</td>
<td>RedHill</td>
</tr>
<tr>
<td>LH011</td>
<td></td>
<td>Pancreatic</td>
<td>Link Health</td>
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</table>
ATAC Technology & Proprietary Projects
ATACs: ADCs with Amanitin as a Payload

Amanitin as Warhead
- Differentiated mechanism of action: inhibition of RNA Polymerase
  - Kills dormant tumor cells
  - Overcomes resistance
  - Predictive biomarker
- Synthetic amanitin derivatives with improved properties
- GMP manufacturing through fully synthetic process

Antibody
- Targeting tumor antigen

Site-specific Conjugation
- Proprietary conjugation sites
- Improved therapeutic index (TI)
- Excellent stability in circulation
The Payload Makes The Difference

Amatoxins – a novel mode of action in oncology

Group of toxins from the poisonous green death cap mushroom (Amanita phalloides)

Amanita phalloides

Amanitins is a specific inhibitor of RNA polymerase II activity:
• The only currently known inhibitor of RNA polymerase II:
  • A new mode of action in oncology
  • All tumors are naïve to it
  • Cell-cycle independent mechanism of action
  • Low intracellular target copies, 1:1 binding

Murine breast cancer xenograft model

• Same antibody (Trastuzumab), different payload (topoisomerase inhibitor vs. amanitin)
• Complete remission after single-dose application of HER2-ATAC.
ATACs Promise Higher Efficacy in Certain Aggressive Tumors

**del(17p) as a potential biomarker for higher ATAC sensitivity**

- Chromosomal deletion that eliminates p53 (higher-risk tumor) and frequently POL2RA gene: lower RNA polymerase II level
- Less amanitin is required to kill these cells: larger therapeutic window

**Clinical relevance:**
- Broad prevalence (ca. 25-60%) across most tumors
- Increased prevalence in advanced and metastatic disease
- Associated with aggressive disease, poor outcomes

**Significance:**
- Higher ATAC efficacy in aggressive tumors with del(17p)
- Use as clinical biomarker in development for patient stratification

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**Collaboration with MD Anderson:**

Higher ATAC sensitivity of del(17p) myeloma cells

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Orlowski et al. MD Anderson ASH 2019
# ATACs Promise Significant Clinical Benefits

## Unique preclinical features of HDP-101

- Efficacious against dormant tumor cells
- Efficacious in ultra-low target-expressing tumor cells
- Novel MoA to which all patients will be naïve
- Ocular toxicity not seen for Amanitin or HDP-101
- Enhanced efficacy in high-risk del(17p) tumors

## Potential clinical benefit

- Longer PFS and MRD negativity
- Deeper responses and higher ORR
- Overcome resistance
- Superior safety profile
- Breakthrough designation and accelerated approval

## ATACs have best-in-class potential
<table>
<thead>
<tr>
<th>Multiple Myeloma (MM)</th>
<th>HDP-101: Anti-BCMA-ATAC</th>
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<tbody>
<tr>
<td>• 70,000 deaths annually</td>
<td>• Targeted elimination of BCMA-containing cells with favorable preclinical toxicity profile</td>
</tr>
<tr>
<td>• Median survival ~47-110 months</td>
<td>• Higher potency in cells with 17p deletions, which are associated with aggressive disease</td>
</tr>
<tr>
<td>• Characterized by the proliferation of single clone of plasma cells derived from B-cells</td>
<td>• Clinical trial started in Feb 2022</td>
</tr>
<tr>
<td>• BCMA (B-cell maturation antigen) overexpression and activation are associated with MM</td>
<td>• Phase I dose escalation study ongoing</td>
</tr>
</tbody>
</table>

**Source:** healthcare-in-europe.com  
**Source:** Heidelberg Pharma
First-in-Human Clinical Trial with an ATAC ongoing
HDP-101: anti-BCMA-ATAC for multiple myeloma

**Trial sites active and enrolling*:**
- MD Anderson, Houston
- Emory University, Atlanta
- Mount Sinai Hospital, New York
- University Hospital Heidelberg
- University Hospital Mainz
- University Hospital Kiel

*Further US and European sites currently being opened

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
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<tbody>
<tr>
<td>2022</td>
<td><strong>Dose escalation</strong> in MM patients: up to 36 patients</td>
</tr>
<tr>
<td>2023</td>
<td><strong>RP2D</strong> Dose for Phase Ila</td>
</tr>
<tr>
<td>2024</td>
<td><strong>Expansion cohorts</strong> BCMA naïve MM Del(17p) stratified</td>
</tr>
<tr>
<td>2025</td>
<td>Two-part, open-label, multicenter Phase I/IIa study to determine safe dose and assess preliminary efficacy</td>
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**Trial status:**
- Three patient cohorts (20, 30, and 60 µg/kg) completed so far, 8 patients in total
- Latest review by Safety Review Committee in March:
  - Treatment is safe and well-tolerated in these three cohorts
  - Continue dose escalation
  - Discussion of Magenta events: no indication that they were related to the ATAC platform
  - Implementation of additional precautionary safety measures recommended to maximize the safety of the patients
Further ATAC Candidates: HDP-102, HDP-103 and HDP-104

**HDP-102: anti-CD37-ATAC**
- CD37 is overexpressed on B-cell lymphoma cells
- Specific indication of non-Hodgkin lymphoma (NHL)
- High prevalence of 17p deletion in NHL
- ASH (Dec 2021): High efficacy of anti-CD37-ATAC in Richter’s syndrome xenograft model

**HDP-103: anti-PSMA-ATAC**
- PSMA is overexpressed in nearly all cases of prostate cancer; limited expression in normal tissue
- Target indication is Metastatic Castration-Resistant Prostate Cancer (mCRPC)
- Prevalence of 17p deletion in mCRPC is 60%
- 17p biomarker has been validated preclinically for prostate cancer (Nature Commun. 2018 22:4394)

**HDP-104: anti-GCC-ATAC**
- Guanylyl cyclase C (GCC) is a transmembrane receptor protein (GUCY2C) for regulation of intestinal electrolyte homeostasis
- (Over-) Expressed in >95% of colorectal cancer, and in ~ 65% of esophageal, gastric, and pancreatic tumors
- Indication: gastrointestinal tumors
- Generating IP and Preparation for preclinical development

Potential IND application in 2024 for HDP-102 and HDP-103
Partner Projects & Next Steps
Partner Projects

Strategic partnership with Huadong Medicine (February/September 2022)

Exclusive licensing agreement for Asia*
- Exclusive development and commercialization rights for HDP-101 and HDP-103; deal value: **up to USD 469 m + royalties**
- Exclusive option for HDP-102 and HDP-104; deal value: **up to USD 461 m + royalties**
- Next 2 ATAC candidates: Right of first negotiation (ROFN)

Investment Agreement
- Equity investment of **€ 105 m** in Heidelberg Pharma
- 2 seats in Supervisory Board

ATAC Technology Collaborations

Research and option agreement for an ATAC with Chiome (July 2022):
Couple amanitin to an antibody that targets CDCP1, expressed on many solid tumors

License agreement for an ATAC with Takeda (September 2022):
Worldwide exclusive license for an ATAC targeting a previously selected target molecule (not disclosed)

* People’s Republic of China, Hong Kong, Macao, Taiwan, South Korea, Indonesia, Singapore, The Philippines, Thailand, Bangladesh, Bhutan, Brunei, Myanmar, Cambodia, Laos, Malaysia, Maldives, Mongolia, Nepal and Vietnam; excludes Japan, India, Pakistan, Sri Lanka
Highlights 2022 - Legacy Portfolio:
Partner Telix - Progressing towards Filing for Market Approval

Pivotal Phase III ZIRCON reported positive topline results with imaging agent TLX250-CDx in November 2022

Accurate diagnosis of clear cell renal cell carcinoma (ccRCC) with TLX250-CDx (89Zr-DFO-girentuximab)

- Global multicenter Ph III trial with 300 patients with renal masses
- Imaging compared to histology of surgically obtained tissue (standard of truth)

Pivotal trial met all endpoints:
- 86% sensitivity, 87% specificity and 93% positive predictive value
- 85% sensitivity and 89% specificity in detecting ccRCC in tumors <4 cm

Next steps:
- Filing for regulatory approval with the FDA and other agencies
- Telix plans with potential marketing approval and launch in 2024
- Indication expansion:
  Ongoing Ph I and II studies in bladder cancer and in triple-negative breast cancer
Financials & Outlook
Financials and Shareholdings

2022

• Sales revenue significantly higher due to upfront payment by Huadong

• Huadong became 2nd largest shareholder, dievini remains largest shareholder

• Operating expenses including depreciation and amortization increased principally because research and development costs increased in line with planning

• Cash reach is secured until mid-2025 based on current budget planning

<table>
<thead>
<tr>
<th>in € m</th>
<th>Actual 2022</th>
<th>Guidance 2023</th>
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</thead>
<tbody>
<tr>
<td>Sales revenue and other income</td>
<td>19.9</td>
<td>7.0 to 10.0</td>
</tr>
<tr>
<td>Operating expenses</td>
<td>37.0</td>
<td>37.0 to 41.0</td>
</tr>
<tr>
<td>Operating result (EBIT)</td>
<td>(17.2)</td>
<td>(28.5) to (32.5)</td>
</tr>
<tr>
<td>Funds required</td>
<td>8.9</td>
<td>32.5 to 36.5</td>
</tr>
<tr>
<td>Funds required per month</td>
<td>0.7</td>
<td>2.7 to 3.1</td>
</tr>
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Next Steps Proprietary ATAC Pipeline
High priority and focus on HDP-101 to advance validation

HDP-101
Phase I/IIa study in RRMM
• Dose escalation ongoing, further study centers in Poland and Hungary
• Implementation of additional precautionary safety measures
• Next dose cohort will be opened with added modifications
• Phase I completion in early 2024 and dose finding for Phase IIa
• Start Phase IIa part in 2024

HDP-102
CD37-ATAC for NHL
• Completion of preclinical and toxicological studies
• IND 2024

HDP-103
PSMA-ATAC for prostate cancer
• Completion of preclinical and toxicological studies
• IND 2024

HDP-104
Guananyl cyclase C (GCC)-ATAC for colorectal cancer
• Focus on generating IP
• Preclinical start in preparation
Investment Summary

A clinical-stage company with the goal of becoming a global ADC player

Disruptive first-in-humans mode of action provides high efficacy and potential for unique clinical advantages

Clinical lead program with best-in-class potential for indication with high medical need

Increased efficacy against certain aggressive tumors based on biomarker

Validated by international high-quality partnerships

Strategic partnership for Asia, fastest growing pharmaceutical market

High value potential with growing ATAC pipeline and attractive ADC environment
Q & A